REMARKS

Claims 1, 3-6, 18-23, 25-28, 31, and 38-49 constitute the pending claims in the present application. Applicants add new claims 39-49. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants cancel, without prejudice, claims 31 and 38. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action. Applicants thank the Examiner and his Supervisor for courtesies extended during an interview conducted at the USPTO on October 7, 2002.

1-2. Applicants note that the amendments filed February 7, 2002 have been entered in full, and that claims 1, 3-5, 18-23, 25-28 and 31 are pending. Applicants additionally point out that new claim 38 was entered in the last response, and accordingly is also currently pending.

Applicants note with appreciation that the finality of the previous office action has been withdrawn. Applicants respectfully request that the fee associated with the Notice of Appeal filed in connection with the final office action be refunded.

3. Applicants acknowledge that any rejection not expressly maintained has been withdrawn.

4. Applicants have corrected the specification to comply with the requirements under 37 CFR 1.821(a)(1) and (a)(2) with regard to the disclosure of nucleic acid and amino acid sequence.

5-6. Claims 1, 3-5, 18-23, 25-28 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

a. Claim 1 is rejected because the recitation of the phrase "cerebral infarct volume" is allegedly inconsistent with the preamble recitation of neuronal cells. To expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended claim 1 to more particularly point out the claimed subject matter. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of the rejection are respectfully requested.

b. The claims are rejected for the recitation of the limitation "at least 50% relative to the absence of administration. Applicants have amended the claims as to the Examiner's suggestion provided on page four of the prior office action where he indicated that "the skilled artisan would reasonably be able to determine an amount effective for reducing cerebral infarct volume in humans." Applicants' amendment is believed to obviate the rejection.

c. The claims are rejected for the recitation of the term "hedgehog polypeptide" without reference to particular sequences. Applicants maintain the arguments of record and contend that hedgehog polypeptides are both well known in the art and extensively described in the specification. Accordingly, one of skill in the art would readily understand the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended the claims to explicitly point out the hedgehog polypeptides for use in the claimed methods. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of the rejection are respectfully requested.

7-8. Claims 1, 3-5, 18-23, 25-28 and 31 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

The specification provides a detailed description of hedgehog signaling, and provides the nucleic acid and amino acid sequences of 3 hedgehog family members isolated from phylogenetically diverse species. Although the hedgehog family members differ in terms of their exact sequence, they share common structural and functional properties. Sonic, Desert and Indian hedgehog all bind to the receptor patched, and the teachings of Pathi et al. demonstrate that the 3 hedgehog family members have the same function in several different in vitro and in vivo models of hedgehog function (Pathi et al., (2001); enclosed herewith as Exhibit 1). Furthermore previous experiments, published prior to the filing of the current application, have demonstrated that murine Sonic hedgehog can function in Drosophila despite the extensive differences in sequence identity between the Drosophila and mouse proteins (Chang et al. (1994); enclosed herewith as Exhibit 2).

Additionally, however, Applicants point out that as of the filing of the present application, the making and testing of polypeptide variants was routine in the art. The Examiner has cited Bowie et al. to support his argument that the variations in polypeptide sequence may have an effect on the function of the protein. While it may be true that variations in sequence may have an effect on the function of a protein, one of skill in the art can readily make and test polypeptide variants and identify those variants that possess the desired function. Given the guidance provided by the specification and the state of the art at the time of filing of the application, the making and testing of variants is nothing more than routine experimentation.

Applicants have provided hedgehog polypeptides from several different species. Additionally, the application provides extensive guidance concerning the making and testing of hedgehog variants (page 30, line 22 to page 36, line 11). Given the guidance provided in the specification, one of skill in the art could readily make a large number of polypeptide variants without undue experimentation.

Furthermore, the claims are explicitly limited to variants which possess specific functional attributes which include the ability to bind patched and the ability to have a specific range of effects on neuronal cell types. Accordingly, one of skill in the art can readily test variant polypeptides to identify polypeptides for use in the subject methods.

Applicants maintain that the claims are enabled throughout their scope. The specification provides a working example which demonstrates the efficacy of hedgehog polypeptides in an adult animal model of stroke. Furthermore, it is well established in the art that Sonic, Desert and Indian hedgehog all bind patched, and that all three hedgehog family members exert similar effects in a wide range of in vitro and in vivo assays. Finally, the specification provides extensive guidance which allows one of skill in the art to make and test polypeptide variants without undue experimentation. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out the claimed subject matter. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

9-10. Claims 1, 3-5, 18-23, 25-28 and 31 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by US Patent No: 5789543. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

The cited reference fails to satisfy the criteria for anticipating the claimed subject matter. Although, as pointed out in the prior Office Action, US 5789543 teaches that ischemia can be treated with a hedgehog polypeptide, "a genus does not always anticipate a claim to a species within the genus." (MPEP 2131.02). Although US 5789543 does recite all of the components of the claimed subject matter (Sonic hedgehog, ischemia, and systemic administration), US 5789543 does not provide one of skill in the art with the necessary guidance to select amongst all of the teachings of the application to arrive at the unique combination of the presently claimed elements. This situation is analogous to the disclosure of a generic chemical formula containing multiple substituents that can vary. Given the generic formula alone, one of skill in the art cannot envisage a structure arrived at by selecting particular substituents independently at each position (In re Petering, 301 F.2d 676 133 USPQ 275 (CCPA 1962).

To provide a specific example, the Court held in *In re Meyer* that the broad disclosure of an alkaline chlorine or bromine solution embraced a large number of species and could not anticipate claims directed to a specific species: alkali metal hypochlorite. (*In re Meyer*, 599 F.2d 1026, 202 USPQ 175 (CCPA 1979)).

Similarly, US 5789543 teaches multiple hedgehog family members, multiple conditions which may be treated by administration of a hedgehog polypeptide, and numerous routes of administration. Given this generic formula, one of skill in the art could not have envisaged the specific combination of elements presently claimed. Accordingly, US 5789543 fails to satisfy the criteria for anticipating the claimed subject matter.

Not only does the cited reference fail to satisfy the criteria for anticipating the claimed subject matter, but the cited reference also fails to render the claimed subject matter obvious. MPEP 2141 provides specific guidance on this point and delineates the criteria that must be satisfied to render an invention obvious in light of the prior art. Most notably, MPEP 2141 states that when evaluating whether an invention is obvious in light of the prior art the invention must be considered as a whole, the prior art must be viewed without the benefit of hindsight, and one must arrive at the claimed subject matter from the prior art with a "reasonable expectation of success." Applicants contend US 5789543 fails to satisfy these criteria.

Applicants contend that a valid patent may issue for a nonobvious species related to a prior patented invention, even though the species falls within the claims of that prior patent. "The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a prima facie case of obviousness." This position is well supported by the MPEP and the holdings of the Federal Circuit. See, for example, *In re Baird,* 16 F.3d 380 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

MPEP 2144.08 provides guidance for examination of claims directed to a species when the prior art teaches the genus. These guidelines require that, based on the disclosure of the prior art reference, one of skill in the art would have been motivated to select the particular species or subspecies from amongst the broad disclosure of the prior art reference. (See for example, *In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995); *In re Deuel* 51 F. 3d).

Furthermore, the standard for rendering an invention obvious is not merely whether one of skill in the art would be motivated to **try** and select a particular species from the genus taught in the prior art. One of skill in the art must have a reasonable expectation of success in arriving at the invention directed to the species. (See for example, In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Though broadly enabling, US 5789543 fails to guide one of skill in the art to specifically select systemic administration from amongst the many routes of administration disclosed in the application. Applicants contend that systemic administration, though generally contemplated in US 5789543, was not the preferred route of administration detailed in that application. Applicants direct the Examiner's attention to column 31, lines 22-31 of US 5789543.

> "Methods of introduction of exogenous *hh* at the site of treatment include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, oral, and intranasal. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir."

Furthermore, Applicants point out that, at the time of filing of the present application, one of skill in the art would not have predicted, with a reasonable expectation of success, that polypeptides administered systemically could cross the blood-brain barrier. Applicants direct the Examiner's attention to a few of the many articles which indicate that at the time of filing of this application, the prevailing notion in the art was that treatment of conditions in the central nervous system required local administration to cells of the CNS such as intrathecal or intraventricular administration (Gash et al. (1998), Eriksdotter et al. (1998), Irving et al. (1996), Tan et al. (1996); enclosed herewith as Exhibits 3-6). Applicants additionally point out that even references published after the filing of the current application indicate that the blood-brain barrier is a substantial impediment to systemic delivery of therapeutic agents to the brain (Lo et al. (2001); enclosed herewith as Exhibit 7). These references serve to illustrate that, at best, it would have been obvious to **try** to administer polypeptides systemically to treat a condition of the central nervous system. However, given the prevailing notion in the art, one of skill in the art could not have predicted, with a reasonable expectation of success, whether polypeptides administered systemically would cross the blood-brain barrier. Accordingly, systemic administration of hedgehog polypeptides to treat conditions of the central nervous system may have been obvious to try in light of US 5789543, however, absent a reasonable expectation of success, obvious to try is an insufficient basis for finding the claimed subject matter obvious in light of US 5789543.

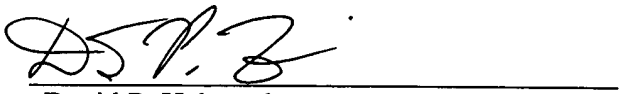
Applicants contend that US 5789543 fails to teach each and every limitation of the pending claims, and accordingly fails to satisfy the criteria for anticipating the claimed invention. Furthermore, Applicants contend that US 5789543 fails to satisfy the criteria for rendering Applicants' invention obvious. A valid patent may issue for a nonobvious species within a prior patented invention, even though the improvement falls within the claims of that prior patent. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same

and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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David P. Halstead
Reg. No. 44,735

Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050